Genetic risk prediction for ten chronic diseases moves closer to the clinic

February 19 2024

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By analyzing millions of small genetic differences across a person's genome, researchers can calculate a polygenic risk score to estimate someone's lifetime odds of developing a certain disease. Over the past decade, scientists have developed these risk scores for dozens of diseases, including heart disease, kidney disease, diabetes, and cancer, with the hope that patients could one day use this information to lower

any heightened risk of disease. But determining whether such tests work effectively across all populations, and how they can guide clinical decision-making, has been a challenge.

Now, a team of researchers at the Broad Institute of MIT and Harvard, in collaboration with 10 academic medical centers across the U.S., has implemented 10 such tests for use in clinical research. In the study published in *Nature Medicine*, the team outlined how they selected, optimized, and validated the tests for 10 common diseases, including heart disease, breast cancer, and type 2 diabetes. They also calibrated the tests for use in people with non-European ancestries.

The scientists worked in collaboration with the national Electronic Medical Records and Genomics (eMERGE) network to study how patients' genetic data can be integrated with their electronic medical records to improve clinical care and health outcomes. The 10 collaborating medical centers enrolled 25,000 participants, while researchers at Broad Clinical Labs, a subsidiary of the Broad Institute, carried out the polygenic risk score testing for those participants.

"There have been a lot of ongoing conversations and debates about polygenic risk scores and their utility and applicability in the clinical setting," said Niall Lennon, chief scientific officer of Broad Clinical Labs, an institute scientist at Broad, and first author of the new paper. "With this work, we've taken the first steps toward showing the potential strength and power of these scores across a diverse population. We hope in the future this kind of information can be used in preventive medicine to help people take actions that lower their risk of disease."

What's the score?

Most polygenic risk scores have been developed based on genetic data largely from people of European ancestry, raising questions about

whether the scores are applicable to people of other ancestries.

To optimize polygenic risk scores for a diversity of people, Lennon and his colleagues first combed the literature looking for polygenic risk scores that had been tested in people from at least two different genetic ancestries. They also searched for scores that indicate a disease risk that patients could reduce with medical treatments, screening, and/or lifestyle changes.

"It was important that we weren't giving people results that they couldn't do anything about," said Lennon.

The team selected 10 conditions to focus on for polygenic risk scores: atrial fibrillation, breast cancer, chronic kidney disease, coronary heart disease, hypercholesterolemia, prostate cancer, asthma, type 1 diabetes, obesity, and type 2 diabetes.

For each condition, the researchers identified the exact spots in the genome that they would analyze to calculate the risk score. They verified that all those spots could be accurately genotyped, by comparing the results of their tests with whole genome sequences from each patient's blood sample.

Finally, the researchers wanted to make polygenic risk scores work across different genetic ancestries. They studied how genetic variants differ across populations by analyzing data from the National Institutes of Health's All of Us research program, which is collecting health information from one million people from diverse backgrounds across the U.S. The team used that information to create a model to calibrate a person's polygenic risk score according to that individual's genetic ancestry.

"We can't fix all biases in the risk scores, but we can make sure that if a

person is in a high-risk group for a disease, they'll get identified as high risk regardless of what their genetic ancestry is," explained Lennon.

With that optimization complete, Lennon's team at Broad Clinical Labs ended up with 10 tests that they are now using to calculate risk scores for the 25,000 people enrolled in the eMERGE study. With their eMERGE collaborators, they are also planning detailed follow-up studies to analyze how polygenic risk scores might influence patients' health care.

"Ultimately, the network wants to know what it means for a person to receive information that says they're at high risk for one of these diseases," Lennon said.

More information: Selection, optimization, and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse populations., *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02796-z

Provided by Broad Institute of MIT and Harvard